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Essential Fatty Acid Transfer and Fetal Development

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Docosahexaenoic acid (22:6n-3) and arachidonic acid (20:4n-6) are important structural components of the central nervous system. These fatty acids are transferred across the placenta, and are accumulated in the brain and other organs during fetal development. Depletion of 22:6n-3 from the retina and brain results in reduced visual function and learning deficits: these may involve critical roles of 22:6n-3 in membrane-dependent signaling pathways and neurotransmitter metabolism. Transfer of 22:6n-3 across the placenta involves specific binding and transfer proteins that facilitate higher concentrations of 22:6n-3 and 20:4n-6, but lower linoleic acid (18:2n-6) in fetal compared with maternal plasma, or in the breast-fed or formula-fed infant. However, human and animal studies both demonstrate that maternal diet impacts fetal 22:6n-3 and 20:4n-6 accretion. After birth, parenteral lipid, human milk and infant formula feeding all result in a marked decrease in plasma 22:6n-3 and 20:4n-6 and an increase in 18:2n-6. Estimation of fetal tissue fatty acid accretion suggests that current preterm infant feeds are unlikely to meet in utero rates of 22:6n-3 accretion. Consideration needs to be given to whether fetal plasma 22:6n-3 and 20:4n-6 enrichment and the low 18:2n-6 facilitates accretion of 22:6n-3 and 20:4n-6 in developing tissues.
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INTRODUCTION

The n-6 and n-3 polyunsaturated fatty acids are essential nutrients that are required for growth and normal cell function. These fatty acids are present in cells as the acyl moieties of phospholipids which make up the structural matrix of cell and subcellular membranes, and function directly, or as precursors to other molecules that modulate cell growth, metabolism, inter- and intracellular communication, protein function and gene expression [1,2]. The n-3 fatty acid docosahexaenoic acid (22:6n-3) is of particular interest because it is selectively accumulated in the membrane amino phospholipids (phosphatidylethanolamine (PE) and phosphatidylserine (PS)) of the retina and brain grey matter [1–4]. Docosahexaenoic acid is accumulated in the brain during brain growth and development; however, 22:6n-3 is also continually turned over, recycled and replenished by uptake from plasma during membrane signal transduction. Many studies have shown that depletion of 22:6n-3 from retinal and neural membranes results in reduced visual function, behavioural abnormalities, alterations in the metabolism of several neurotransmitters, and decreased membrane protein, receptor and ion channel activities [1,2]. Recent studies have also shown G-protein coupled receptor signaling, including the activity of phosphodiesterase, is decreased by depletion of 22:6n-3 from retinal rod outer segment membranes [5].

The n-6 and n-3 fatty acids cannot be formed de novo by mammalian cells; thus all of the n-6 and n-3 fatty acids accumulated by the fetus must ultimately be derived from the mother by placental transfer, and after birth all must be provided by the infant diet. The n-6 and n-3 fatty acids recognized as essential dietary nutrients are linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3), respectively, and these fatty acids are formed in plant, but not animal cells [1,2]. Once obtained from the diet, 18:2n-6 and 18:3n-3 can be further desaturated and elongated by Δ6 desaturase, elongation and Δ5 desaturase to arachidonic acid (20:4n-6) and eicosapentaenoic acid (20:5n-3) from 18:2n-6 and 18:3n-3, respectively. Synthesis of 22:6n-3 proceeds by successive elongation of 20:5n-3 to 24:5n-3, followed by desaturation at position 6 to 24:6n-3, and chain shortening to 22:6n-3 [1,2]. Synthesis of 22:5n-6 from 20:4n-6 occurs in an analogous pathway. Unlike 18:2n-6, 18:3n-3 is not known to have any essential biological functions in humans; rather the biological role of n-3 fatty acids appears to be fulfilled by 20:5n-3 and 22:6n-3.

Placental transfer of 20:4n-6 and 22:6n-3 is believed to involve a multi-step process of uptake and intracellular translocation that is facilitated by several membrane-associated

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and cytosolic fatty acid binding proteins; these proteins favour n-6 and n-3 fatty acids over non-essential fatty acids, and 20:4n-6 and 22:6n-3 over 18:2n-6 or 18:3n-3 [6–10]. However, although the relative proportions of 20:4n-6 and 22:6n-3 in plasma lipids are higher in the fetus than in the mother, the maternal dietary intake of n-6 and n-3 fatty acids does influence the transfer of these fatty acids to the fetus [11,12]. This paper focuses on the importance of maternal dietary fatty acids to the transfer of n-6 and n-3 fatty acids to the fetus, n-6 and n-3 fatty acid transport in fetal plasma, and the implications for the feeding of prematurely born infants.

Placental transfer and fetal lipid transport of n-6 and n-3 fatty acids

As introduced above, all of the n-6 and n-3 fatty acids accumulated by the fetus are derived by transfer across the placenta and ultimately originate from the maternal diet. The n-6 and n-3 fatty acids may be provided as 20:4n-6 and 22:6n-3, or as their 18:2n-6 and 18:3n-3 precursors, respectively. Experimental studies have shown that placental fatty acid transfer involves diffusion as well as membrane and cytosolic fatty acid binding proteins; membrane binding proteins that favour n-6 and n-3 fatty acids over non-essential fatty acids and 20:4n-6 and 22:6n-3 over 18:2n-6 and 18:3n-3 may be important in facilitating placental transfer of the latter longer chain n-6 and n-3 fatty acids to the fetus [6–10]. Recent reviews of placental fatty acid transfer have been published [9,13,14]. The Δ6 and Δ5 desaturases are present in fetal liver from early in gestation, but the activity of these enzymes appears to be low before birth [1,15–18]. Further, experimental studies have clearly shown that preformed 22:6n-3 provided in the maternal diet is much more efficacious than 18:3n-3 as a source of n-3 fatty acids for fetal tissue 22:6n-3 accretion [19–23]. Similarly, although desaturation of 18:3n-3 to 22:6n-3 occurs in infants and adults, including preterm infants, the activity of the pathway appears to be low with <1–9% 18:3n-3 converted to 22:6n-3 [24–27]. There is no evidence that the ability to form 20:4n-6 from 18:2n-6 is low in humans, although providing a source of preformed 20:4n-6 in the diet increases plasma and red blood cell phospholipid 20:4n-6 in adults and infants [28–30], and increases tissue 20:4n-6 in animals [31,32].

Analyses of the n-6 and n-3 fatty acids in maternal and fetal plasma (cord blood collected immediately following term birth) has shown that the relative proportions of 20:4n-6 and 22:6n-3 are higher, while 18:2n-6 is lower in triglycerides, phospholipids and cholesterol esters in the fetal than maternal plasma (Table 1). Similarly, 20:4n-6 and 22:6n-3 represent a higher proportion while 18:2n-6 is lower in the unsaturated fatty acids of fetal plasma esterified lipids than in the plasma of one-month-old breast-fed infants or infants fed formula (Table 2). However, despite higher proportions of 20:4n-6, 18:2n-6 is clearly transported across the placenta. The contribution of preferential acylation of 20:4n-6 and 22:6n-3 into esterified lipids released by the placenta to the fetal circulation and of specificity of acyltransferases involved in triglyceride and phospholipid synthesis in fetal liver to the high proportions of 20:4n-6 and 22:6n-3 in fetal plasma is not yet known. In this regard, recent studies have shown that the placenta secretes apo B containing particles in the low density lipoprotein (LDL) density range [33], suggesting that the placenta could contribute to the molecular species of phospholipids, triglycerides and cholesterol esters characteristic of fetal plasma lipids. In addition, both Δ6 and Δ5-desaturase have been identified in the placenta [34,35]; thus it is possible that placental synthesis of 20:4n-6 from 18:2n-6 could contribute to 20:4n-6 in the fetal circulation. The unusual distribution of fatty acids in fetal plasma esterified lipids includes about 40% 20:4n-6 in cholesterol ester fatty acids whereas about 80% of cholesterol esters in maternal plasma are esterified with 18:2n-6 (Figure 1). After birth,

Table 1. Concentrations of linoleic acid (18:2n-6), α-linolenic acid (18:3n-3), arachidonic acid (20:4n-6) and docosahexaenoic acid (22:6n-6) in maternal and fetal plasma

	Triglyceride	Phospholipid	Cholesterol ester
18:2n-6			
Maternal	13.7 ± 0.5 (*7.8–26.2*)	20.8 ± 0.4 (*13.6–27.2*)	42.4 ± 0.7 (33.2–56.7)
Fetal	10.1 ± 0.4 (2.9–17.0)	7.7 ± 0.2 (5.2–10.7)	15.6 ± 0.4 (9.0–22.7)
18:3n-3			
Maternal	1.2 ± 0.1 (0.4–3.8)	0.4 ± 0.0 (0.2–0.8)	1.0 ± 0.1 (0.1–2.6)
Fetal	0.5 ± 0.0 (0.2–1.0)	0.1 ± 0.0 (0.0–0.2)	1.2 ± 0.1 (0.4–3.8)
20:4n-6			
Maternal	0.9 ± 0.0 (0.5–2.1)	8.7 ± 0.2 (5.6–11.8)	5.3 ± 0.1 (2.5–8.4)
Fetal	3.6 ± 0.2 (1.0–7.3)	17.7 ± 0.2 (13.8–23.0)	11.8 ± 0.4 (2.1–17.4)
22:6n-3			
Maternal	0.5 ± 0.0 (0.2–1.4)	5.0 ± 0.2 (2.8–8.1)	0.7 ± 0.0 (0.1–1.4)
Fetal	2.8 ± 0.2 (0.5–5.9)	7.7 ± 0.2 (4.4–11.7)	1.4 ± 0.1 (0.6–3.1)

Maternal plasma was collected at 35 weeks gestation (n = 58) and fetal plasma was collected immediately following term delivery (n = 70). Blood for 12 pregnant women from whom fetal cord blood was collected was not available for analyses. Results are means ± SEM (range), wt% total fatty acids.